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Ivermectin treatment in humans for reducing malaria transmission (Review)

de Souza DK, Thomas R, Bradley J, Leyrat C, Boakye DA, Okebe J

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TABLE OF CONTENTS

[Intervention Review]

Ivermectin treatment in humans for reducing malaria transmission

Dziedzom K de Souza[1a], Rebecca Thomas[2b], John Bradley[3], Clemence Leyrat[4], Daniel A Boakye[1], Joseph Okebe[5]

[1]Noguchi Memorial Institute for Medical Research, College of Health Sciences, University of Ghana, Accra, Ghana. [2]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. [3]MRC International Statistics and Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK. [4]Medical Statistics Department, London School of Hygiene & Tropical Medicine, London, UK. [5]Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK

[a]These authors contributed equally to this work. [b]These authors contributed equally to this work

Contact address: Dziedzom K de Souza, ddesouza@noguchi.ug.edu.gh.

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ABSTRACT

Background

Malaria is transmitted through the bite of *Plasmodium*-infected adult female *Anopheles* mosquitoes. Ivermectin, an anti-parasitic drug, acts by killing mosquitoes that are exposed to the drug while feeding on the blood of people (known as blood feeds) who have ingested the drug. This effect on mosquitoes has been demonstrated by individual randomized trials. This effect has generated interest in using ivermectin as a tool for malaria control.

Objectives

To assess the effect of community administration of ivermectin on malaria transmission.

Search methods

We searched the Cochrane Infectious Diseases Group (CIDG) Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, Science Citation index - expanded, the World Health Organization (WHO) International Clinical Trials Registry Platform, ClinicalTrials.gov, and the National Institutes of Health (NIH) RePORTER database to 14 January 2021.

We checked the reference lists of included studies for other potentially relevant studies, and contacted researchers working in the field for unpublished and ongoing trials.

Selection criteria

We included cluster-randomized controlled trials (cRCTs) that compared ivermectin, as single or multiple doses, with a control treatment or placebo given to populations living in malaria-endemic areas, in the context of mass drug administration. Primary outcomes were prevalence of malaria parasite infection and incidence of clinical malaria in the community.

Data collection and analysis

Two review authors independently extracted data on the number of events and the number of participants in each trial arm at the time of assessment. For rate data, we noted the total time at risk in each trial arm. To assess risk of bias, we used Cochrane's RoB 2 tool for cRCTs. We documented the method of data analysis, any adjustments for clustering or other covariates, and recorded the estimate of the intra-cluster correlation (ICC) coefficient.

We re-analysed the trial data provided by the trial authors to adjust for cluster effects. We used a Poisson mixed-effect model with small sample size correction, and a cluster-level analysis using the linear weighted model to adequately adjust for clustering.

Main results

We included one cRCT and identified six ongoing trials.

The included cRCT examined the incidence of malaria in eight villages in Burkina Faso, randomized to two arms. Both trial arms received a single dose of ivermectin 150 µg/kg to 200 µg/kg, together with a dose of albendazole. The villages in the intervention arm received an additional five doses of ivermectin, once every three weeks. Children were enrolled into an active cohort, in which they were repeatedly screened for malaria infection.

The primary outcome was the cumulative incidence of uncomplicated malaria in a cohort of children aged five years and younger, over the 18-week study. We judged the study to be at high risk of bias, as the analysis did not account for clustering or correlation between participants in the same village.

The study did not demonstrate an effect of Ivermectin on the cumulative incidence of uncomplicated malaria in the cohort of children over the 18-week study (risk ratio 0.86, 95% confidence interval (CI) 0.62 to 1.17; P = 0.2607; very low-certainty evidence).

Authors' conclusions

We are uncertain whether community administration of ivermectin has an effect on malaria transmission, based on one trial published to date.

PLAIN LANGUAGE SUMMARY

Malaria control using ivermectin

What is the aim of this review?

The aim of this Cochrane Review was to find out if giving the drug ivermectin to entire communities could reduce malaria transmission. We examined all relevant studies to answer this question, and found one relevant study.

Key messages

It is not possible to say at this point if treating an entire community with ivermectin reduces malaria. Several research studies are in progress; we anticipate they will provide more answers in the future.

What was studied in the review?

Malaria is a disease transmitted to humans through the bite of mosquitoes infected with *Plasmodium* parasites. It results in nearly half a million deaths every year. Ivermectin is a drug that is given to whole communities to control the parasites that are responsible for elephantiasis and river blindness. It has been observed that ivermectin can kill mosquitoes when they feed on the blood of people who have taken this medication. Therefore, it is believed that by giving this drug to whole communities, it will kill many mosquitoes, and could reduce malaria transmission.

In this review, we assessed whether treating entire communities with ivermectin would reduce malaria transmission. We looked for studies from different sources, and only included studies that took place in communities with malaria, and that randomly assigned groups of people to ivermectin or a control, which could be a placebo or standard community drug treatments. We wanted to know if the treatment influenced the occurrence of malaria in the community.

What are the main results of the review?

One study met the inclusion criteria. This study included eight villages in Burkina Faso, which were randomly assigned to receive ivermectin or a control. All villages received ivermectin, as part of the scheduled control of lymphatic filariasis. In addition, the treatment villages received five more doses of ivermectin, once every three weeks. The effect of ivermectin on malaria was measured in children younger than five years of age. In these children, the treatment did not show a notable difference in the presence of malaria between the treatment and control groups (very low-certainty evidence).

Therefore, it is not possible to say at this point if the treatment of entire communities with ivermectin has an effect on reducing malaria. Several studies are currently ongoing; we anticipate they will provide more answers in the future.

How up-to-date is this review?

We searched for studies published up to 14 January 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Ivermectin versus control in humans to reduce malaria transmission

Ivermectin treatment in humans for reducing malaria transmission

Patient or population: adults and children living in malaria-endemic areas

Setting: villages in Burkina Faso
Intervention: single dose ivermectin 150 µg/kg to 200 µg/kg + 400 mg albendazole + 5 additional doses of ivermectin

Comparison: single dose ivermectin 150 µg/kg to 200 µg/kg + 400 mg albendazole

Outcome	Anticipated absolute effects		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard community MDA programmes	Risk difference with repeated ivermectin MDA (95% CI)				
Incidence of clinical malaria *Follow-up: 18 weeks*	2460 per 1000	344 fewer per 1000 (from 935 fewer to 418 more-)	Risk ratio (RR) 0.86 (0.62 to 1.17)	590 (1 cRCT)	⊕⊖⊖⊖ Very low[a,b,c]	We are uncertain whether or not repeat mass ivermectin administration reduces malaria incidence.
Adverse events *Follow-up: 18 weeks*	19 per 1000	12 more per 1000 (0 fewer to 32 more)	RR 1.63 (1.00 to 2.67)	2712 (1 cRCT)	⊕⊖⊖⊖ Very low[d,e]	We are uncertain whether or not repeat mass ivermectin administration results in more adverse events.

CI: confidence interval; **MDA**: mass drug administration; **cRCT**: cluster-randomized controlled trial; **RR:** risk ratio.
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[a]Downgraded by two levels for risk of bias: due to bias arising from the timing of identification and recruitment of individual participants, and bias in the selection of the reported result.
[b]Downgraded by one level for imprecision: a small number of clusters, CIs span from fewer to more episodes of malaria.

[c]Downgraded by one level for indirectness: outcome was uncomplicated malaria, measured in children only.
[d]Downgraded by two levels for risk of bias: bias arising from the timing of identification and recruitment of individual participants, and bias in the selection of the reported result.
[e]Downgraded by one level for imprecision: low number of events and the CIs meet the line of no effect.

BACKGROUND

Malaria is an important vector-borne disease, with an estimated 229 million cases and 409,000 deaths annually (WHO 2020). It is caused by infection with the *Plasmodium* parasite. *Plasmodium falciparum and Plasmodium vivax* are the main *Plasmodium* species that cause persistent blood-stage infections in humans, which last several weeks and months (Ashley 2014). In sub-Saharan Africa, the main mosquito species responsible for transmission are *Anopheles gambiae sensu stricto*, *An funestus*, and *An arabiensis*. *An gambiae sensu stricto* is considered the most efficient of the malaria vectors, and preferentially feeds on humans (Hay 2004).

Preventing mosquito bites is key to controlling malaria infection, and the use of long-lasting insecticide-treated bed nets (LLINs) and indoor residual spraying (IRS) with insecticides are central to this strategy (Killeen 2014; Russell 2013). About 57% of people living in sub-Saharan Africa now have access to a treated bed net (WHO 2019a). Compared to estimates at the beginning of the century, the global incidence of malaria cases and deaths has significantly declined, with a 44% reduction in deaths in the World Health Organization (WHO) African region (WHO 2020). It is estimated that vector control interventions contributed to averting over 600 million clinical cases between 2000 and 2015 (Bhatt 2015).

Although progress in malaria control has slowed, the significant reduction in disease burden has prompted optimism for progress towards elimination in areas where reductions have been substantial, and for accelerating control measures to prevent a resurgence in transmission (WHO 2020). The large scale use of drugs and insecticides for elimination also raises concerns about increasing resistance to interventions considered the mainstay of control strategies. Insecticide resistance can manifest as changing vector behaviour in response to insecticide exposure, such as insecticide avoidance, outdoor biting preferences, and early exit behaviour by indoor-feeding vectors (Killeen 2014; Sougoufara 2014; Thomsen 2017). These vector behaviour changes reduce the effectiveness of vector control interventions.

Additional interventions and strategies are clearly needed to sustain the gains made (Feachem 2019; WHO 2019b), and contain the spread of resistant vectors and parasites (Churcher 2016; Riveron 2016).

Given that a competent vector needs to live long enough to allow parasite development in the vector and subsequent transmission to a human host, reducing the survival and fitness of mosquitoes is important for the control of malaria transmission. The incubation period of *P falciparum* in the mosquito is between 12 and 18 days, at temperatures of about 24 °C (Blanford 2013). Furthermore, the reproductive cycle of the mosquito, from blood feeding, blood meal digestion, egg maturation, to laying eggs, is shorter than the period of parasite development in the mosquito (Clements 1992). In *An gambiae* mosquitoes, the reproductive cycles could be as short as two days (Quiñones 1997). Thus, female mosquitoes that live long enough to transmit parasites are more likely to have achieved reproductive success (Sy 2014).

Therefore, increasing the mortality rate of infected mosquitoes could significantly reduce the risk of transmission. One such method is the use of systemic insecticides or endectocides (used for the control of both endoparasites and ectoparasites). Ivermectin, a microfilaricide used for the control of veterinary and human helminths, but toxic to mosquitoes, has shown great potential (Derua 2015).

Description of the condition

Malaria transmission involves stages of growth and development in both humans and the mosquito vector. Strategies to control transmission are either preventive or therapeutic, and target parasite stages in humans or the mosquito vector (Graves 2018; Sinclair 2009).

Interventions against the mosquito vector rely on the biting and resting behaviours of mosquitoes (Paaijmans 2011). For example, insecticides on LLINs and IRS are designed for contact with the mosquito while indoors. They do not affect the parasite directly, but shorten the lifespan of the mosquito vector, thus, they interrupt the progression of the parasite cycle.

Interventions intended to have an impact on malaria transmission must be delivered on a large scale, for effect. These mass drug treatment campaigns have been implemented in the past as part of malaria elimination programmes (Nájera 2011). Mass drug administration (MDA) involves treating entire populations in a geographical area with a therapeutic dose of a drug, regardless of the presence of symptoms, and without the need to determine infection status. Following reductions in the global malaria burden, there has been renewed interest in MDA to reduce malaria transmission (Newby 2015; Poirot 2013).

Description of the intervention

Ivermectin is a broad-spectrum, anti-parasitic drug, used extensively for the treatment of a number of parasites in animals and humans (Burg 1979). In humans, it is mainly used in the treatment of onchocerciasis and lymphatic filariasis (Brown 2000; Cupp 2011), and is delivered through mass treatment campaigns (Makunde 2003; Molyneux 2003).

Ivermectin binds selectively and strongly to glutamate-gated, chloride ion channels in muscles and nerve cells of invertebrates (Meyers 2015), and increases the permeability of their cell membrane to chloride ions. This process disrupts gamma-aminobutyric acid (GABA)-mediated neurosynaptic transmission in the central nervous system, resulting in flaccid paralysis and death (Ikeda 2003). While humans lack the specific glutamate-gated channels that bind ivermectin, GABA-gated channels are expressed that might cross-react with ivermectin (Wolstenholme 2012). Nonetheless, ivermectin is generally considered safe in humans, but toxic to organisms, such as mosquitoes.

Ivermectin is readily absorbed in humans following ingestion (Edwards 1988), and reaches peak plasma concentrations within four hours (Elkassaby 1991). However, it is quickly metabolized, with a half-life of about 18 hours (Merck 2009). Ivermectin is widely distributed in the body, mostly in fatty tissue (González Canga 2008), and high concentrations have been observed in individuals with raised body mass index (Ouédraogo 2015).

Ivermectin is not recommended in areas co-endemic for *Loa loa*, as serious adverse reactions, including encephalopathy, extrapyramidal neurological signs, and in extreme cases, death, have been associated with its use (Boussinesq 2001; Gardon 1997). Ivermectin is also not recommended for use by pregnant women (Nicholas 2020), and children younger than five years (Farrar 2013).

Ivermectin, the prototype endectocide, could have a role in mass treatment towards malaria elimination (Chaccour 2010; Derua 2015). In order to accelerate the re-purposing of ivermectin for malaria control and elimination, the WHO Global Malaria Programme published the preferred product characteristics for the use of endectocides as alternative interventions for controlling malaria transmission (WHO 2017a). A WHO technical consultation meeting recommended a 20% target reduction in malaria incidence for one month after MDA with a single round of ivermectin alone, or a significant reduction in malaria incidence for up to 12 months post-intervention, if used in combination with artemisinin-based combination therapy (ACT), and core vector control interventions for malaria control, as benchmarks for impact (WHO 2017b).

How the intervention might work

Background

Ivermectin may reduce malaria transmission by shortening the lifespan of *Anopheles* mosquitoes exposed to the drug. For impact, the endectocidal effect must be sustained long enough to limit vector capacity. This can be achieved by giving higher doses, multiple doses, or using slow-release preparations. However, the efficacy must be balanced against the risk of side effects, which may increase at higher doses (Chaccour 2017). Modelling studies have predicted that ivermectin could have a significant effect when used alone, or as a complementary intervention, in high transmission settings, in areas suitable for elimination, and may be most effective in areas with short transmission seasons (Slater 2020). However, these models are based on data using laboratory-reared mosquitoes, which may behave differently compared to wild mosquitoes (Slater 2020).

The endectocidal effect of ivermectin has been studied mainly by in vitro experiments, where lab-reared mosquitos feed on ivermectin preparations via a membrane, and by in vivo studies, where mosquitos are allowed to feed on individuals' blood after they have taken oral ivermectin (Alout 2014; Chaccour 2015; Derua 2015; Foley 2000; Kobylinski 2011). These studies demonstrate that the effect on mosquito mortality depends on the concentration of the drug in the blood, and the length of time drug concentrations remain above the lethal threshold. Sublethal effects of ivermectin have also been described, and include delayed re-feed time, inhibiting the development of sporozoites, and reductions in fertility and egg hatch rates (Chaccour 2017). Endectocidal and sub-lethal outcomes in these studies have been reported in different formats, which creates a challenge for interpreting the effect.

Systematic review of randomized controlled trials of ivermectin on mosquito mortality

The main Cochrane Review assesses the ability of ivermectin to reduce malaria transmission in the community.

However, to assess the evidence behind the theory that ivermectin may have an effect on transmission, we briefly present our systematic review of the evidence that ivermectin has an effect on mosquito mortality. The full details of this systematic review are in Appendix 1.

Our inclusion criteria were randomized controlled trials (RCTs), conducted in healthy or malaria-infected people, who were given oral ivermectin, and then either gave blood for membrane feeding, or allowed *Anopheles* species mosquitoes to feed directly on their arms. Studies measured cumulative mortality in the mosquitoes that were given access to the blood through membrane or direct feeding. We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 14 January 2021, Issue 1 of 12) in the Cochrane Library (searched 14 January 2021), MEDLINE Pubmed (1946 to 14 January 2021), Embase Ovid, (1974 to 14 January 2021), and Web of Science (searched 14 January 2021), using the search terms: ivermectin or avermectin OR abamectin) AND Anopheles or mosquitocid*. Two review authors (RT and JO) applied the inclusion criteria, and resolved any discrepancies by discussion. We used tabular data to summarise the outcome measures, as time points and mortality measures are highly variable.

We identified 198 articles, five of which we included (Chaccour 2010; Derua 2015; Mekuriaw 2019; Ouédraogo 2015; Smit 2018). In these studies, participants received oral ivermectin, after which, feeding experiments, using laboratory-reared mosquitoes were conducted at set time points. The data showed that ivermectin has a large effect on mosquito mortality. This effect was associated with the dose of ivermectin, and the time between the ingestion of ivermectin and the feeding experiment. The effect also appeared to differ with mosquito species. A full summary of the results are presented in Appendix 1.

These findings are consistent with results from non-randomized studies and ivermectin-based MDAs against other mosquito-borne diseases, such as lymphatic filariasis and onchocerciasis (Alout 2014; Kobylinski 2011; Kositz 2017; Sylla 2010; Tesh 1990).

Why it is important to do this review

There is a need for consensus in determining and defining outcome measures, methods for data analysis, and interpretation of results, to support decisions on the role of ivermectin in reducing malaria transmission in endemic populations.

Our systematic review of five published studies showed a consistent and dose-dependent effect of oral ivermectin treatment in humans on mosquito mortality (Appendix 1). The studies also found that the observed mosquito mortality decreased as the time following ivermectin ingestion increased. Higher doses of ivermectin prolonged this effect, indicating a longer time of lethal concentration of ivermectin in the participants' blood.

However, it is unclear whether this translates to reduced malaria transmission in endemic populations with wild mosquito vectors. In addition, the association between entomological endpoints, such as mosquito mortality and epidemiological indicators of impact, have not been validated. Other factors, such as bed net and insecticide usage, may affect the effectiveness of the intervention.

Presently, there is one published trial on the effect of oral ivermectin on malaria transmission (Foy 2019), and a number of Ongoing studies, with results expected in forthcoming years. This Cochrane Review provides a critique of the existing study, and highlights considerations for data analysis and presentation of results from subsequent trials, which will support a comprehensive update of this review.

OBJECTIVES

To assess the effects of community administration of ivermectin on malaria transmission.

METHODS

Criteria for considering studies for this review

Types of studies

We included cluster-randomized controlled trials (cRCTs) that compared mass administration of ivermectin to either infected or uninfected people versus control or standard mass drug regimes given to the whole population. Studies in which ivermectin was administered to animals were considered if there was simultaneous administration to the human population.

Because the interventions considered in this review are at the community level, and the primary outcomes are population-based malaria transmission indices, cRCTs are the most appropriate design to estimate unbiased causal effects at the level of communities, which are relevant for policymakers.

Types of participants

We included adults and children living in malaria-endemic areas.

Types of interventions

Intervention

Community mass drug administration (MDA) of ivermectin, given alone or together with other treatments, as single or multiple doses**.**

Control

Placebo or no treatment.

Other drugs administered as part of the usual MDA programme in the study area, as long as they were given to both intervention and control arms. Ivermectin was considered an appropriate control if this was part of the existing drug administration programme in the study area, and differed in dose from the intervention arm.

Types of outcome measures

The primary outcome measures were amended prior to the screening process to prioritize population-based outcomes important for health policy.

Primary outcomes

- Prevalence of malaria parasite infection measured by microscopy, rapid diagnostic tests (RDTs), or molecular methods
- Incidence of clinical malaria, defined by symptoms with parasitaemia, detected by microscopy or RDTs

Secondary outcomes

- Mosquito mortality or survival at one, three, and nine days post-treatment
- Mosquito density (number of each mosquito species in the study area, determined by trapping experiments)
- *P falciparum* sporozoite rates (the proportion of female anopheline mosquitoes with *P falciparum* sporozoites in their salivary glands)
- *P falciparum* oocyst rates (the proportion of female anopheline mosquitoes with *P falciparum* oocysts in their gut)

Adverse effects

- Serious adverse effects (deaths, disability, hospitalization)
- Other adverse events, which may be local or systemic, but do not meet a classification as serious)

Search methods for identification of studies

We searched for all relevant studies regardless of date, language, or publication status.

Electronic searches

The Cochrane Infectious Diseases Group (CIDG) Information Specialist searched the following databases, using the search terms detailed in Appendix 2: the CIDG Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL, 2021, Issue 1), in the Cochrane Library (searched 14 January 2021); MEDLINE PubMed (1966 to 14 January 2021); Embase OVID (1947 to 14 January 2021); Latin American Caribbean Health Sciences Literature (LILACS BIREME; 1982 to 14 January 2021); and Science Citation index - Expanded Web of Science (1900 to 14 January 2021), We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/); ClinicalTrials.gov (clinicaltrials.gov/); and the National Institutes of Health (NIH) RePORTER database (projectreporter.nih.gov/reporter.cfm), using (ivermectin OR avermectin OR abamectin) and (malaria OR mosquit*).

Searching other resources

We checked the reference lists of the included study for other potentially relevant studies. We contacted researchers working in the field to ask about unpublished and ongoing trials.

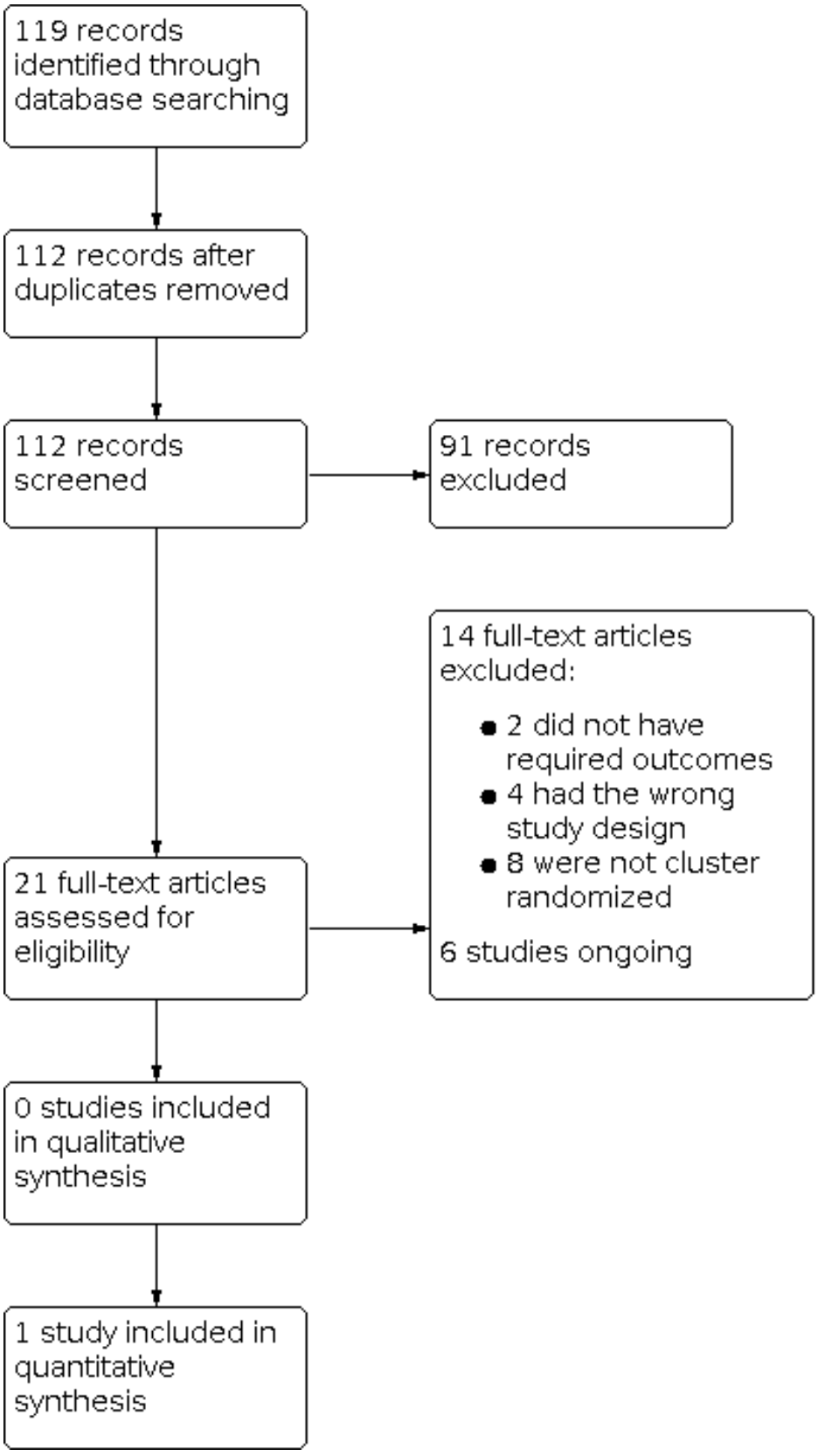
We searched the MESA Track: a living database of research projects focusing on malaria eradication, to find unregistered trials in progress (www.malariaeradication.org/mesa-track; searched 8 February 2021).

Data collection and analysis

Selection of studies

Two review authors (DKD and JO) independently screened the titles and abstracts of the search results for potentially relevant studies, using predefined eligibility criteria. We reviewed the full-text of reports identified through this screening, and resolved disagreements on eligibility by discussion. We considered duplicate publications from the same study as a single entry. We listed all studies excluded after full-text assessment in a Characteristics of excluded studies table. The selection process is presented in a PRISMA diagram (Figure 1).

Figure 1. PRISMA flow diagram detailing the database search results and study selection process



Data extraction and management

Two review authors (DKD and RT) independently extracted data using a pre-tested extraction form, with differences in extracted data resolved in discussion with a third review contributor (Dr Birhanu Ayele). In order to evaluate causes of heterogeneity, we extracted data on study design; study population and setting (country); frequency of ivermectin administration; duration of follow-up for both human and mosquito populations; and methods for ensuring comparability between sites in multisite studies. We also extracted estimates of outcomes of interest, together with their corresponding measures of precision for our meta-analysis.

For dichotomous variables, we extracted data on the number of events and the number of participants in each trial arm at the time of assessment. For rate data, we extracted the number of events in the treatment and comparison group, and the total time at risk in each trial arm. For cRCTs, we recorded the unit of randomization, the number of clusters, and the average size of each cluster. We documented details about adjustment for clustering or other covariates, such as the intra-cluster correlation (ICC) coefficient. We contacted the study authors for additional information when this was unclear in the trial report.

Assessment of risk of bias in included studies

Four review authors (CL, RT, DKD, and JO) independently assessed the risk of bias of the included studies, using Cochrane's RoB 2 for cRCTs (Eldridge 2021). When there were differences in judgments, we came to a group consensus, including review authors RT, JO, and DKD. We used the ROB 2 tool for cRCTs Microsoft Word template, November 2020 version, to complete the assessment (Sterne 2019). We assessed the risk of bias for intention-to-treat effects for the primary outcomes, malaria incidence and adverse events. We assessed items under the following domains:

- Risk of bias in the randomization process
- Bias in the timing of identification and recruitment of individual participants in relation to the timing of randomization
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in the measurement of the outcome
- Bias in the selection of the reported result

We reported the judgements as 'low', 'some concerns', or 'high'. We generated a summary risk of bias table based on our observations using the Risk-of-bias VISualization (robviz) tool (McGuinness 2020). The recorded consensus decisions are stored as supplemental data. We judged studies to have a high risk of bias when we judged one domain to be at high risk of bias, or where we found some concerns in multiple domains, unless we could justify a different judgment.

Measures of treatment effect

We compared the incidence of clinical malaria episodes by calculating the risk ratio and the mean difference in rates of episodes between treatment arms. We presented effect estimates with 95% confidence intervals (CIs).

We compared the frequency of adverse events between treatment arms as absolute numbers, risk ratios, and risk differences with 95% CIs.

Unit of analysis issues

The search focused on cRCTs only, so we sought to account for clustering (at the level used for randomization) in the analysis, in order to obtain valid CIs and P values. For trials with a small number of clusters, we applied specific small sample corrections to avoid an inflation of the type I error rate, that is, a too high probability of showing a statistically significant intervention effect when there is none (Kahan 2016; Leyrat 2017).

In the included trial, these considerations were ignored, hence, we re-analysed the data using a Poisson mixed-effects model with a small-sample correction to compare rates of malaria episodes between clusters (units of randomization (Kenward 1997)).

For repeated treatment given to the same participant, we analysed outcomes as count outcomes. We did not include the same participant's data in a meta-analysis more than once, to avoid double-counting. To account for variations in treatment effect between individual studies, we considered using a random-effects model for any planned meta-analysis.

Dealing with missing data

We searched for discrepancies in the published data on participant numbers and percentage loss for each treatment group. When all randomized participants were accounted for, we conducted an intention-to-treat analysis.

Assessment of heterogeneity

We assessed the baseline characteristics of included studies to determine the suitability of pooling the results in a meta-analysis. We planned to regard heterogeneity as moderate if the I^2 statistic lay between 30% and 60%; substantial if it was between 59% and 90%; and considerable if it was between 75% and 100% (Deeks 2017). We would regard a Chi^2 test statistic with a $P \leq 0.10$ to be indicative of statistically significant heterogeneity. We planned an exploration of clinical and methodological heterogeneity through consideration of the trial populations, methods, and interventions, and by visualization of trial results. When we found heterogeneity that was at least moderate, we planned a subgroup analysis to help identify any effect modification observed in the result.

Assessment of reporting biases

We could not assess reporting bias since we only included one trial in the review. We assessed selective outcome reporting in the included trial as part of the risk of bias assessment.

Data synthesis

We only included one study in the review, but were able to obtain the primary data from the trial authors, which we re-analyzed.

When additional trial results become available, we will combine study data in a meta-analysis, if feasible. When appropriate, we will combine studies with a fixed-effect meta-analysis model, based on the generic inverse-variance approach. However, we will use a random-effects model in the event of considerable heterogeneity (I^2 statistic over 75%). We will present results for unadjusted cRCTs separately if we do not have enough information to adjust them for clustering. For outcomes of repeated dosing, we will

stratify the analysis by the number of rounds of treatment. The primary analysis will pool data regardless of risk of bias.

Subgroup analysis and investigation of heterogeneity

We did not conduct a subgroup analysis. In future revisions, we will evaluate heterogeneity in results by subgroup analysis based on malaria transmission intensity (i.e. low- or high-density infection areas), population treated and assessed for malaria (i.e. children versus adults), and ivermectin dose and frequency of administration (single or multiple doses versus annual or biannual administration).

Sensitivity analysis

For each study, we analyzed the primary outcome using a Poisson regression model with a random effect, to account for clustering at the level of the unit of randomization, with the Kenward-Roger correction for small samples (Kenward 1997). To assess the robustness of the results to different modelling assumptions, we re-analysed the trial data using:

- a cluster-level analysis of the difference in rates of malaria episodes using a weighted t-test, with weights accounting for the variability in cluster size. This approach is very robust when only a few clusters are randomized.
- a random-effect Poisson regression without a small sample correction, to check the impact on power of the small sample correction
- generalized estimating equations (GEEs) with an exchangeable correlation structure, with and without a small sample correction, to estimate population-average, rather than cluster-specific effects (Huang 2016).

When additional trial results become available, we will conduct a sensitivity analysis to assess the effects of restricting the analysis to trials with low or low plus some concerns in the risk of bias assessment.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Schünemann 2013). We appraised the certainty of the evidence in relation to the following criteria: study design, risk of bias, inconsistency, indirectness, imprecision, other considerations (including publication bias).

We generated a summary of findings table for our primary outcomes when data was available and adverse events, using GRADEpro GDT (GRADEpro GDT).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We identified 119 records through our searches. We removed duplicates, leaving 112 records and we screened all articles for possible inclusion. After title and abstract screening, we excluded 91 ineligible trials. We assessed 21 full-text articles for eligibility and excluded 14 articles for the following reasons: two trials did not have the required outcomes, four had the wrong study design, and eight were not cluster-randomized. One trial met the inclusion criteria with six identified ongoing trials (Figure 1).

Included studies

One study met the inclusion criteria (Foy 2019). This was a cluster-randomized pilot study conducted in Burkina Faso, a malaria-endemic country with highly seasonal transmission (Ouédraogo 2013). Study villages were the unit of randomization, and a total of eight villages were included in the study; four villages per arm. This trial was registered as a pilot study, and powered as such.

Participants in both trial arms received a single dose of ivermectin 150 µg/kg to 200 µg/kg, together with a dose of albendazole, as part of the scheduled control of lymphatic filariasis. Villages in the intervention arm received an additional five doses of ivermectin, one every three weeks (Foy 2019). The primary outcome, cumulative malaria incidence, was measured in a cohort of children, aged five years and younger. Malaria prevalence was not measured in this trial.

In total, 563 (20.7%) of the study village population were excluded from MDA for various reasons; height less than the required 90 cm, pregnant women, nursing mothers within the first week of birth, and people with a history of travel to a *Loa loa* endemic area. Of the children in the primary outcome monitoring cohort, 21% (121 of 590) met the criteria to receive ivermectin.

The primary outcome was the cumulative incidence of uncomplicated malaria, measured in the cohort of 590 children (263 children in the control villages and 327 children in the intervention villages) over an 18-week intervention period. An uncomplicated malaria episode was defined as a child with a temperature of at least 38.0°C, or a history of fever in the preceding 24 hours, and a positive malaria rapid diagnostic test. Other measured outcomes were: the passive case detection of the number and type of adverse events following ivermectin ingestion, and serological reactivity to anopheline salivary gland protein. Entomological outcomes included human biting rate, sporozoite rate, entomological inoculation rate, and mosquito parity.

We contacted the study authors for the use of the primary data for re-analysis. The lead author kindly supplied and approved the use of the primary data.

Excluded studies

We excluded 14 studies, and listed the reasons in the Characteristics of excluded studies.

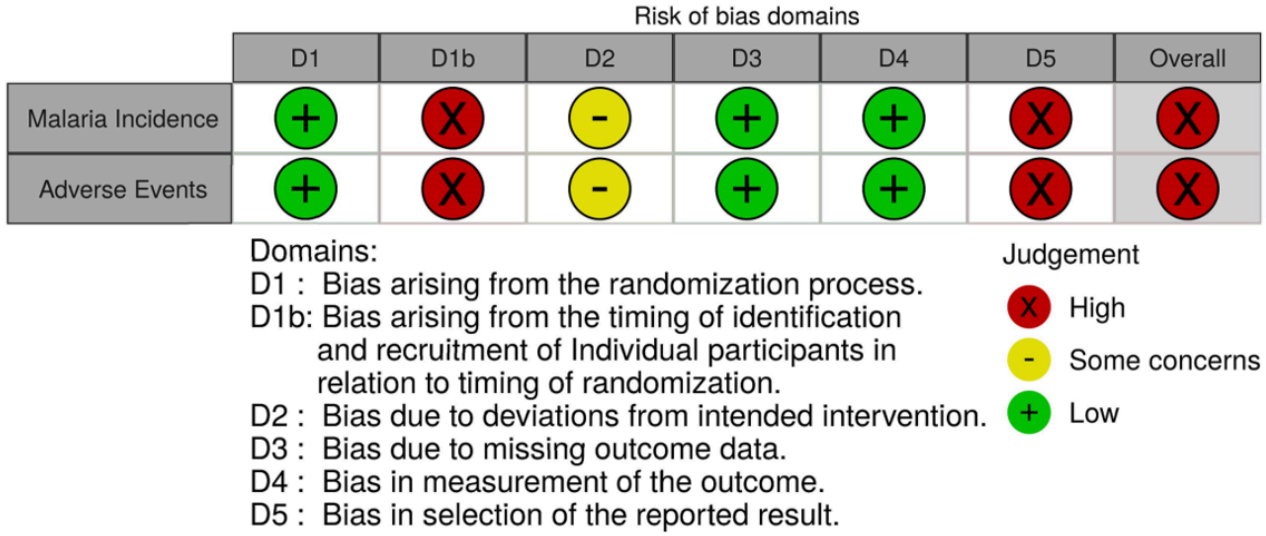
Ongoing studies

We identified six ongoing studies in the trials registers (Rabinovich ongoing; NCT04844905 (MATAMAL); NCT03074435 (REACT); NCT03576313 (MASSIV); NCT03967054 (RIMDAMAL II); PR150881). See details in Characteristics of ongoing studies.

Risk of bias in included studies

Please see Figure 2 for the risk of bias summary. A supplementary file containing details of the RoB 2 consensus judgments is available on request from the CIDG editorial base.

Figure 2. Summary of risk of bias for each outcomes, across domains



For the primary outcome of malaria incidence, we judged the study to have an overall high risk of bias, due to the high risk of bias in the identification or recruitment of participants in the cRCT, and in the selection of the reported result. The enrolment of individual participants took place after randomization, and we judged that knowledge of the decision could have influenced participation. Baseline imbalances in bed net use could represent differential recruitment, however, with a few clusters, the imbalances could be due to chance (Table 1). We judged there to be a high risk of bias due to multiple eligible measurements of malaria incidence, and multiple analyses of the data.

We had some concerns due to deviations from the intended interventions. The participants were not blinded to the intervention. However, the dropout rates were low with 79% of participants in the control villages and 75% of the participants in the intervention villages. No whole clusters were analysed in a group different from their allocation.

We judged there to be a low risk of bias arising from the randomization process, along with adequate allocation concealment. We judged there to be a low risk of bias due to low levels of missing outcome data, with 14 out of the 263 children recruited from the control villages and 10 of the 327 children from the intervention villages lost to follow-up. We judged there to be a low risk of bias in the measurement of the main outcome; this was standardized and the outcome assessors were blinded to the intervention received. See Table 2 for a summary of the RoB 2 judgments and justifications for malaria incidence.

For the outcome adverse events, we also judged it at an overall high risk of bias, due to the identification of participants after randomization, and the selection of the reported result. We noted an additional concern in the reporting of the significance of the adverse event risk difference. The trial authors did not report the P value for the adverse event risk difference of 1.21, 95% CI 0.04 to 2.38; the values suggest a significant increase in adverse events. However, as we judge the risk ratio to be the primary effect estimate, this did not affect our overall risk of bias judgment. See Table 3 for a summary of the RoB 2 judgments and justifications for adverse events.

Effects of interventions

See: **Summary of findings 1** Ivermectin versus control in humans to reduce malaria transmission

Primary outcomes

Prevalence of malaria parasite infection

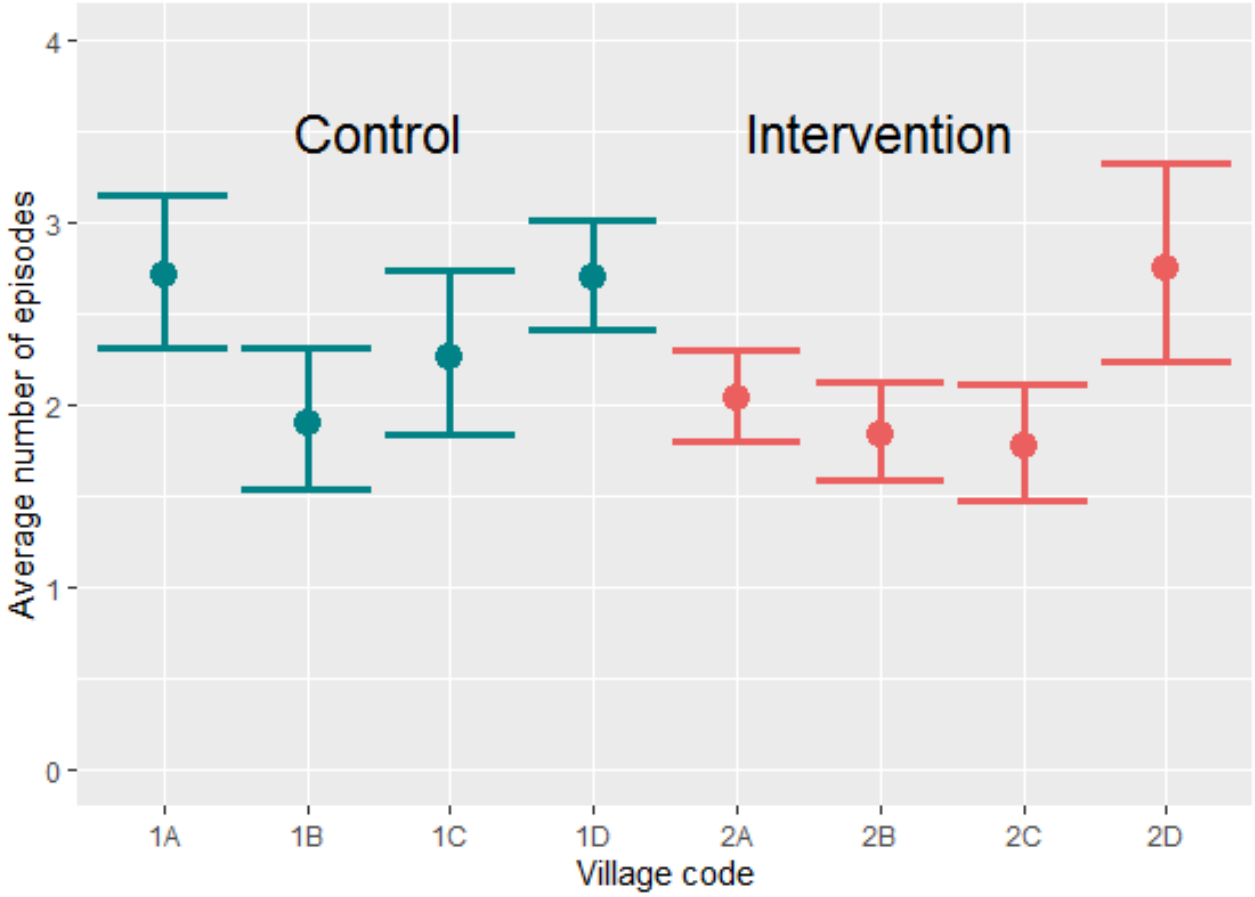
No included trials reported the effect of mass administration of ivermectin on the prevalence of malaria parasite infection.

Incidence of clinical malaria

Foy 2019 reported 648 malaria episodes in the intervention group (327 children) and 647 episodes in the control group (263 children). We present the results using different models of analysis appropriate for cRCTs with small number of clusters.

The risk ratio (RR) of malaria episodes between the intervention and the control arms, when estimated using the Poisson mixed-effects model with small sample size correction, was 0.86 (95% CI 0.62 to 1.17; P = 0.2607). The mean difference (MD) in the rate of malaria episodes between arms when using the Poisson mixed model with small-sample correction was -0.35 (95% CI -1.05 to 0.36; P = 0.2617). The mean difference in malaria episodes in the cluster level analysis using weights accounting for variability in cluster size was -0.34 (95% CI -0.90 to 0.22; P = 0.2829). Figure 3 demonstrates the overlap of CIs of the malaria rates between each cluster.

Figure 3. Distribution of the average number of malaria episodes per cluster.



Secondary outcomes

Mosquito mortality or survival

No included trials measured the effect of mass administration of ivermectin on mosquito mortality or survival.

Mosquito density

No included trials measured the effect of mass administration of ivermectin on mosquito density.

P falciparum sporozoite rates

The study authors did not share the sporozoites rate data for re-analysis but reported in the published report that it was not noticeably different between groups.

The reported weekly entomological inoculation rate was not different between the control and intervention arms (P = 0.956). The study authors did not report the effect size, nor did they share the data for reanalysis.

P falciparum oocyst rates

No included trials measured the effect of mass administration of ivermectin on *p falciparum* oocyst rates.

Adverse effects

The trial authors did not provide us with safety data for re-analysis, so we reported on the trial results presented in the published report, which are unadjusted for the clustering effect.

The reported risk of adverse events among all participants was higher in the intervention group than in the control group. The study reported 45 events (3%) from 1447 participants in the intervention group, and 24 events (2%) from 1265 in the control group. The risk ratio (RR) was 1.63, 95% CI 1.01 to 2.67; P = 0.060. Sixty-nine adverse events occurred in 65 (2%) participants who reported one episode adverse event, and 4 (0.1%) participants who reported a second event. Thirty-two (49%) of these adverse events were reported from the cohort of children.

The study authors deemed the adverse events that were classified as possibly or probably related to the intervention as adverse reactions. There were five (0.3%) adverse reactions in the intervention group, and three (0.2%) in the control group. These included vomiting, pruritus, oedema in the limbs, and tremors. There were 20 (0.7%) deaths amongst all participants during the trial period, which were deemed unlikely or not related to the intervention.

DISCUSSION

There is considerable interest in the use of ivermectin to complement existing malaria control interventions. Individual-based studies using laboratory-reared mosquitoes provide a proof-of-concept on the efficacy of ivermectin for mosquito mortality (Appendix 1). Modelling studies suggest that ivermectin can reduce malaria transmission when used in combination with other antimalarials (Slater 2020). However, currently, there is only one published cluster-randomized controlled trial (cRCT) that has assessed the role of ivermectin in reducing malaria transmission (Foy 2019). This trial was registered as a pilot study and powered as such.

Summary of main results

We included one cluster-randomized controlled trial (cRCT). The study was conducted in Burkina Faso, with eight villages randomized to two arms. Both trial arms received a single dose of ivermectin 150 µg/kg to 200 µg/kg, together with a dose of albendazole. Villages in the intervention arm received an additional five doses of ivermectin, one every three weeks. Children, aged five years and younger, were enrolled in an active cohort, in which they were repeatedly screened for malaria infection.

The primary outcome was the cumulative incidence of uncomplicated malaria in the cohort of children, over the 18-week study. The study did not demonstrate an effect of ivermectin on the cumulative incidence of uncomplicated malaria in the cohort of children over the 18-week study (risk ratio 0.86, 95% confidence interval (CI) 0.62 to 1.17; P = 0.2607), although the study was underpowered to detect the true effect.

Overall completeness and applicability of evidence

While models of potential effect have been used to inform possible applications of the drug, the study included in this Cochrane Review did not demonstrate an effect of ivermectin on the cumulative incidence of uncomplicated malaria. The benefits of the intervention could be detected through future adequately powered studies. There are a number of ongoing studies, which could improve our understanding of the effectiveness of this intervention (see Characteristics of ongoing studies).

Quality of the evidence

We assessed the certainty of the evidence using the GRADE approach, and presented it in the Summary of findings 1.

There was very low-certainty evidence about the efficacy of ivermectin in reducing the incidence of clinical malaria. The effect estimate was based on a single trial with a high risk of bias. Bias arose from the timing of identification and recruitment of individual participants, and bias in the selection of the reported result. This study was conducted as part of the scheduled yearly mass treatment activities with ivermectin, which is relatively safe, and has been given in Burkina Faso since the early 2000s. Therefore, there may be potential biases due to participants' knowledge of the drug and response to the intervention, compared to participants who had not taken this drug before. Baseline imbalances in bed net use and the number of children could represent differential recruitment, although, this could also be compatible with chance with cluster randomization. The multiple possible analyses of the final result introduces bias.

We also downgraded due to imprecision, due to the small number of clusters and overlapping CIs. The effect is indirect, as the outcome was uncomplicated malaria, measured in children ≤ 5 years, most of whom would not have received the treatment due to the ≥ 90 cm height requirement.

We judged the certainty of the evidence about the safety of ivermectin to be very low because of imprecision, due to a low number of events and a CI that included no effect.

Potential biases in the review process

We re-analysed the primary data. We investigated potential bias by conducting a sensitivity analysis using the three available approaches for analysis when there is a small sample size in a cluster-randomized trial.

We included only cluster-randomized trials, and this resulted in the exclusion of several cohort or cross over trials that reported some of the secondary outcomes. We have, however, included the RCT data in Appendix 1.

Agreements and disagreements with other studies or reviews

There has been no other systematic review conducted on this topic. A narrative review by the Ivermectin Roadmappers 2020 included Foy 2019 as the only study to demonstrate the effect of ivermectin MDA on malaria transmission. In the review they quoted a 20% reduction in malaria incidence in children < 5 years old but acknowledge the debate over the statistical significance of these findings, which was highlighted as inappropriate (Bradley 2019). For the mosquito lethal efficacy data, they included trials in which mosquitoes bloodfed on animal as well as human blood donors (Ivermectin Roadmappers 2020). This highlighted the variation in mosquito lethal effects for ivermectin, depending on the bloodmeal source.

We re-analysed the primary study data provided by the trial authors. The methods that we used for the re-analysis to account for clustering are, to our knowledge, all the available methods for the analysis of cluster RCT's with a small sample size and all showed consistent results. The consistent lack of effect in the reanalysis differs from the findings in the original publication. This lack of effect may be from a lack of power and not a lack of benefits from the intervention.

We cannot make a conclusive inference on the effect of ivermectin on malaria transmission based on this single trial. However, it highlights the importance of the process used in generating trial results for reported outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Although ivermectin has been demonstrated to reduce the lifespan of *Anopheles* mosquitoes (Appendix 1), we do not know if community administration of ivermectin has an effect on malaria transmission.

The available evidence on the effect of ivermectin on malaria transmission comes from one published trial (Foy 2019). The intervention did not show an effect in reducing the cumulative

incidence of uncomplicated malaria. Therefore, we are uncertain whether community administration of ivermectin reduces malaria transmission.

Implications for research

The results of this trial, published in the Lancet, were contested based on differences in the analytical protocol used in presenting the primary outcome results (Bradley 2019; Foy 2019 (Foy 2019 Authors' reply)). It is important that ongoing trials consider and adopt a consistent protocol for analysis in cRCTs to improve our confidence in the effectiveness of ivermectin in malaria transmission.

While children under five years of age are considered most vulnerable to disease, transmission is more likely to be sustained via the older population, who are typically asymptomatic carriers (Bousema 2014; Lindblade 2013). Other trials reporting on the incidence and prevalence of infection would be useful in addressing the question of possible herd effect in the community.

There are a number of trials in progress addressing the question of whether community administration of ivermectin reduces malaria transmission; the results will be included in updates of this review when available (Rabinovich ongoing; NCT04844905 (MATAMAL); NCT03074435 (REACT); NCT03576313 (MASSIV); NCT03967054 (RIMDAMAL II); PR150881). See details in Characteristics of ongoing studies.

There is some uncertainty about what entomological outcomes are critical for making public health decisions and; recommendations, and how these should be measured. Comparative data from ongoing trials could help address this.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Foy 2019

Study characteristics	
Methods	**Study design:** cluster-randomized controlled trial (cRCT) **Study grouping:** parallel groups
Participants	**Inclusion criteria:** Individuals resident in study village, who consented to receive ivermectin and albendazole in a mass drug administration (MDA) campaign **Exclusion criteria:** children shorter than 90 cm, pregnant women, breastfeeding mothers with a baby within 1 week of birth, a history of travel to an area endemic for *Loa loa* **Malaria transmission intensity at study site:** hyper-endemic **Risk of contracting malaria:** high **Demographics:** ***Age*** Intervention: median 16 years (6 to 35 years) Control: median 14 years (7 to 30 years) ***Sex*** Intervention: male 713 (49%), female 734 (51%) Control: male 620 (49%), female 645 (51%) ***Bed net use*** Intervention: 1369 (95%)

Foy 2019 *(Continued)*

	Control: 1094 (86%) ***Coverage of MDA*** Intervention: 75% in round 1; 73% in round 2, 3, and 4; 72 in round 5, and 70% in round 6 Control: 79% in the single round
Interventions	Single dose ivermectin 150 µg/kg to 200 µg/kg with 400 mg albendazole given to both groups, followed by five further doses of ivermectin at 3-week intervals to intervention group only
Outcomes	**Human outcomes** • Cumulative incidence of uncomplicated malaria episodes over the 18-week intervention period in the cohort of children aged 5 years or younger (main outcome) • Number and type of adverse events among enrolled participants, obtained by passive case detection • Parasitaemia, multiplicity of infections (number of different *P falciparum* clones in each infection), force of infection • Serological reactivity to an anopheles salivary gland protein • Prevalence of soil-transmitted helminthes in children aged 6 to 10 years **Entomological outcomes** • Human biting rate (number of mosquitoes that blood-fed or attempted to blood-feed per person per week) • Sporozoite rate (proportion of captured mosquitoes infected with sporozoites) • Entomological inoculation rate (product of the human biting rate and the sporozoite rate) • Proportion of parous mosquitoes • Presence of *Wuchereria bancrofti* in captured mosquitoes
Identification	**Sponsorship source:** Grand Challenges Explorations programme grant, the Bill & Melinda Gates Foundation **Country:** Burkina Faso **Setting:** Community-based **Comments:** **Authors name:** Prof Brian D Foy **Institution:** Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology, and Pathology, Colorado State University **Email:** brian.foy@colostate.edu **Address:** Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO 80523–1692, USA
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alout 2014	Wrong study design

Study	Reason for exclusion
Bockarie 1998	Wrong outcomes
Chaccour 2009	Not a cRCT
Chaccour 2010	Not a cRCT
Derua 2015	Not a cRCT
de Souza 2017	Wrong outcomes
Kobylinski 2011	Not a cRCT
Kobylinski 2017	Wrong study design
Kositz 2017	Wrong study design
Mekuriaw 2019	Not a cRCT
NCT02511353	Not a cRCT
Ouédraogo 2015	Not a cRCT
Pinilla 2018	Wrong study design
Smit 2018	Not a cRCT

RCT = randomized controlled trial; cRCT = cluster-randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT03074435 (REACT)

Study name	Insecticide resistance management in Burkina Faso and Côte d'Ivoire (REACT)
Methods	cRCT, parallel assignment
Participants	Number: 18000; clusters: not stated
Interventions	1) insecticidal paints, 2) larvicides, 3) ivermectin for both human and domestic animals, and 4) strengthened Information, Education and Communication (IEC) strategy to complement the universal coverage with LLINs
Outcomes	*Primary outcome measures:* 1. Malaria incidence (time frame: continuous monitoring for 2 years) Malaria cases reported in local health system *Secondary outcome measures:* 1. Entomological inoculation rate (time frame: every 8 weeks for 2 years) Number of infectious bites/person 2. Malaria prevalence (Time frame: every 4 months for 2 years) % of positive blood smears among the population between 6 months to 20 years

NCT03074435 (REACT) *(Continued)*

Starting date	27 January 2010
Contact information	Cédric Pennetier, PhD Institut de Recherche pour le Développement
Notes	Location: Burkina Faso and Côte d'Ivoire Registration number: NCT03074435 Source of funding: Expertise France

NCT03576313 (MASSIV)

Study name	Mass drug administration of ivermectin and dihydroartemisinin-piperaquine as an additional intervention for malaria elimination (MASSIV)
Methods	Cluster-randomized, parallel-assignment trial
Participants	Village residents aged 6 months and older, all genders
Interventions	Intervention clusters: mass drug administration (MDA) with ivermectin (IVM) and dihydroartemisinin-piperaquine (DP) given to eligible participants plus the National Malaria Control Program standard malaria control intervention Control clusters: only standard malaria control interventions as implemented by the National Malaria Control Program
Outcomes	*Primary outcomes*: • Prevalence of malaria infection determined by molecular methods • Vector parous rate *Secondary outcomes*: • Malaria prevalence at the peak of the first transmission season • Incidence of clinical (laboratory confirmed) malaria cases • Serological markers of recent malaria • Serological markers of recent Anopheles exposure • Mosquito density • Mosquito mortality • Sporozoite rates in field-caught mosquitoes
Starting date	August 2018
Contact information	Umberto D'alessandro, MD, PhD +220-4495443-6 ext 4001; udalessandro@mrc.gm (PI)
Notes	clinicaltrials.gov/ct2/show/NCT03576313 **Location:** Gambia, Basse Villages **Registration number:** NCT03576313 Source of funding: MRC Unit, The Gambia

NCT03967054 (RIMDAMAL II)

Study name	Repeat Ivermectin Mass Drug Administrations for MALaria control II (RIMDAMAL II)
Methods	cRCT, parallel assignment
Participants	Number: 4700; clusters: not stated Description: eligible village population in southwestern Burkina Faso over two consecutive rainy seasons eligible to receive MDA. Observe the effect for reducing the incidence of uncomplicated malaria episodes in enrolled village children (≤ 10 years of age) assessed by active case surveillance
Interventions	Mass administration of ivermectin or placebo will be given monthly over 4 months of each rainy season to the eligible village population, each as 3-day course of 300 µg/kg/day
Outcomes	*Primary outcome measure*: • Malaria incidence (time frame: up to 8 months) *Secondary outcome measures:* • Adverse events (time frame: up to 25 months) • Blood-fed mosquito mortality (time frame: up to 8 months) • Entomological inoculation rate (time frame: approximately 8 months over 2 consecutive rainy seasons (2019 to 2020)) • Human antibody responses to an Anopheles salivary gland peptide (time frame: up to 8 months) • *Plasmodium* prevalence (time frame: up to 8 months) • *Plasmodium* parasitaemia (time frame: up to 8 months) • *Plasmodium* multiplicity of infection (time frame: up to 8 months) • *Plasmodium* molecular force of infection [time frame: up to 8 months)
Starting date	13 July 2019
Contact information	Catherine Bens 970-491-5445; Cat.Bens@colostate.edu Contact: Tammy Felton-Noyle 970-491-1655: Tammy.Felton-Noyle@colostate.edu
Notes	**Location:** Burkina Faso **Registration number:** NCT03967054 **Source of funding:** National Institute of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)

NCT04844905 (MATAMAL)

Study name	Adjunctive Ivermectin Mass Drug Administration for Malaria Control (MATAMAL): a cluster randomised placebo-controlled trial
Methods	Phase three trial. Ivermectin will be compared to dihydroartemisinin-piperaquine (DP) treatment only in a cluster-randomized community-based trial in the Bijagós archipelago of Guinea-Bissau
Participants	Guinea-Bissau Islands
Interventions	MDA Ivermectin

NCT04844905 (MATAMAL) *(Continued)*

Outcomes	*Primary outcome*: population-based *Plasmodium falciparum* prevalence (all ages)
Starting date	2019
Contact information	Anna Last London School of Hygiene & Tropical Medicine Keppel Street London WC1E 7HT
Notes	Funding Details Medical Research Council (MRC), UK Wellcome Trust Department for International Development (DFID), UK Department for International Development (DFID), UK

PR150881

Study name	A novel vector control measure to combat the spread of Artemisinin resistance in the Greater Mekong Subregion
Methods	Two cRCTs, parallel assignment
Participants	Number: not stated; clusters: not stated
Interventions	(1) a two-arm trial to assess the impact of three ivermectin MDAs spaced 1 month apart in three villages compared to three control villages, and (2) a three-arm trial to assess the impact of three dihydroartemisinin-piperaquine plus primaquine with and without ivermectin MDAs spaced 1 month apart with each regimen distributed to two villages compared to two control villages
Outcomes	Parameters of malaria transmission • Epidemiological (malaria prevalence, gametocytaemia, resistant parasite ratios, and haemoglobin concentrations) • Entomological (vector composition, density, sporozoite rate, resistant parasite ratios, and blood meal composition)
Starting date	30 September 2016
Contact information	Prachumsri, Jetsumon Mahidol University
Notes	Location: the Greater Mekong Subregion Registration number: PR150881 Source of funding: CDMRP

Rabinovich ongoing

Study name	BOHEMIA: Broad One Health Endectocide-based Malaria Intervention in Africa
Methods	Two double-blinded cRCTs
Participants	Number: not stated; clusters: not stated Description: Tanzania and Mozambique - during the malaria season; people and animals
Interventions	Ivermectin
Outcomes	*Primary outcome:* mosquito survival up to 28 days post blood-feeding *Secondary outcome*: ivermectin plasma concentration ng/L
Starting date	February 2019 to February 2023
Contact information	Regina Rabinovich Director of the Malaria Elimination Initiative; regina.rabinovich@isglobal.org
Notes	Location: Tanzania and Mozambique Registration number: Not registered Source of funding: Unitaid

ADDITIONAL TABLES

Table 1. Baseline characteristics of the children, clusters, and households

	Control N = 263	**Intervention N = 327**	**Standardized mean difference (%)***
Individual-level covariates	n (%)	n (%)	
Male	120 (45.6)	159 (48.6)	6
Bednet use	229 (87.1)	314 (96.0)	32.6
Age 4 to 5 years	92 (35.0)	136 (41.6)	13.6
Height ≥ 90 cm	61 (23.2)	69 (21.1)	12.9
Age (median (Q1 to Q3)) , years	3 (1 to 4)	3 (1 to 4)	
Cluster-level covariate	**N = 4**	**N = 4**	
Number of included children per village	43, 48, 58, 114	35, 66, 98, 128	

Table 1. Baseline characteristics of the children, clusters, and households *(Continued)*

Households	N = 106	N = 127
Household size (median (Q1 to Q3))	2 (1 to 3)	2 (1 to 3)

*The standardized mean difference is a measure quantifying the imbalance between groups. A variable with a difference > 10% between groups is considered unbalanced.

Table 2. RoB 2 for cluster-randomized trials summary of judgments: malaria Incidence

1a.1. Was the allocation sequence random?	Y	Low risk	Sealed envelopes containing the words 'treatment' and 'control' were mixed in a container and randomly pulled from the container by a community health worker representing each village. There were large baseline imbalances in bednet use; however, these differences could be due to chance.
1a.2. Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?	Y		
1a.3. Were there baseline imbalances that suggest a problem with the randomization process?	PN		
1b.1. Were all the individual participants identified before randomization of clusters?	N	High risk	Enrolment of households took place after the randomization of villages. Knowledge of multiple mass drug administrations (MDA) could affect participant decision-making. Heads of households discussed with the chiefs whether to be involved in the study or not. See protocol pg 25. The baseline imbalance in bednet use and the number of children could represent differential recruitment. However, this could be compatible with chance with cluster randomization.
1b.2. If N/PN/NI to 1b.1: is it likely that selection of individual participants was affected by knowledge of the intervention?	NI		
1b.3. Were there baseline imbalances that suggest differential identification or recruitment of individual participants between arms?	PN		
2.1a. Were participants aware that they were in a trial?	Y	Some concerns	The study was blinded only to the outcome-assessor, who was allowed access only to the coded group and participant data when doing the initial analyses. The participants or carers were not blinded to the intervention. Deviations from the intended intervention were not reported.
2.1b. If Y/PY/NI to 2.1a: were participants aware of their assigned intervention during the trial?	Y		
2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y		
2.3. If Y/PY/NI to 2.1 or 2.2: were there deviations from the intended intervention that arose because of the trial context?	NI		
2.4. If Y/PY to 2.3: were these deviations from intended intervention unbalanced between groups	NA		

Table 2. RoB 2 for cluster-randomized trials summary of judgments: malaria Incidence *(Continued)*

and likely to have affected the outcome?			
2.5a. Were any clusters or participants analysed in a group different from the one to which they were assigned?	NA		
2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI		
2.7. If N/PN/NI to 2.6: was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	N		
3.1a. Were outcome data available for all, or nearly all, clusters randomized?	Y	Some concerns	Data were available for all clusters randomized. 14 children were lost to follow-up from the control group, and 10 from the intervention group. Data were available in all clusters. "Participation in mass drug administrations in the intervention group started at 1080 (75%) of 1447 enrolled village residents and dropped slightly over subsequent administrations: 1056 (73%) in the second, 1051 (73%) in the third, 1060 (73%) in the fourth, 1037 (72%) in the fifth, and 1020 (70%) in the sixth administration. In the control group, 999 (79%) of 1265 people participated in the mass drug administration." There was a fall in coverage in the intervention arm, however, as the control had no placebo, it is difficult to say if the deviations arose because of the trial context. They did not state whether they compared a per-protocol analysis or ITT analysis.
3.1b. Were outcome data available for all, or nearly all, participants within clusters?	Y		
3.2. If N/PN/NI to 3.1: are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA		
3.3. If N/PN/NI to 3.1: is there evidence that results were robust to the presence of missing outcome data?	NA		
4.1. Was the method of measuring the outcome inappropriate?	N	Low risk	The method of measuring malaria incidence is acceptable in public health malaria trials. The outcome (cumulative incidence of uncomplicated malaria episodes in children ≤ 5 years of age) was assessed by active case surveillance in study villages 2X/week – a malaria episode was defined as ≥ 38.0 °C fever or a history of fever in the last 24 hours + positive rapid diagnostic test for *Plasmodium falciparum*. There was an objective protocol for measurement. The study was blinded only to the outcome assessor, who was allowed access only to the coded group and participant data when doing the initial analyses. The outcome assessor was defined as the assessor conducting the analysis. It was unlikely that the awareness of the outcome assessor would have influenced the outcome measurement.
4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N		
4.3a. If N/PN/NI to 4.1 and 4.2: were outcome assessors aware that a trial was taking place?	Y		
4.3b. If Y/PY/NI to 4.3a: were outcome assessors aware of the intervention received by study participants?	N		

Table 2. RoB 2 for cluster-randomized trials summary of judgments: malaria Incidence *(Continued)*

5.1. Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	High risk	There was a prespecified analysis plan, however, it did not detail the method of cluster adjustment used. They used clinical malaria -definition uncomplicated only. Malaria episode was defined by a temperature of 38.0°C or higher (0.5°C was added to each thermometer recording to account for axillary readings) or history of fever in the last 24 h, and a positive rapid diagnostic test (SD Bioline Malaria Ag P.f/Pan; Alere, Inc) for *Plasmodium*. Rapid diagnostic tests were considered positive if any test line appeared (histidine-rich protein II antigen of *P falciparum*, or common lactate dehydrogenase of *Plasmodium sp*, or both), and incidence data were not modified in response to these results. As demonstrated in the review, the method of adjustment can influence the results.
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...			
5.2. ...multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y		
5.3 ...multiple eligible analyses of the data?	Y		

Y: Yes; N: No, PY: Probably Yes, PN: Probably No, NI: No Information

Table 3. RoB 2 for cluster-randomized trials summary of judgments: adverse events

1a.1. Was the allocation sequence random?	Y	Low risk	Sealed envelopes containing the words 'treatment' and 'control' were mixed in a container and randomly pulled from the container by a community health worker representing each village. There were large baseline imbalances in bednet use; however, these differences could be due to chance.
1a.2. Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?	Y		
1a.3. Were there baseline imbalances that suggest a problem with the randomization process?	PN		
1b.1. Were all the individual participants identified before randomization of clusters?	N	High risk	Enrolment of households took place after the randomization of villages. Knowledge of multiple mass drug administrations (MDA) could affect participant decision-making. Heads of households discussed with the chiefs whether to be involved in the study or not. See protocol pg 25. The baseline imbalance in bednet use, and the number of children could represent differential recruitment. However, this could be compatible with chance with cluster randomization.
1b.2. If N/PN/NI to 1b.1: is it likely that selection of individual participants was affected by knowledge of the intervention?	PY		
1b.3. Were there baseline imbalances that suggest differential identification or recruitment of individual participants between arms?	N		

Table 3. RoB 2 for cluster-randomized trials summary of judgments: adverse events *(Continued)*

2.1a. Were participants aware that they were in a trial?	Y	Some concerns	The study was blinded only to the outcome assessor, who was allowed access only to the coded group and participant data when doing the initial analyses. The participants or carers were not blinded to the intervention. Deviations from the intended intervention were not reported. Although 14 children were lost to follow-up from the control group and 10 from the intervention groups. "Participation in mass drug administrations in the intervention groups started at 1080 (75%) of 1447 enrolled village residents and dropped slightly over subsequent administrations: 1056 (73%) in the second, 1051 (73%) in the third, 1060 (73%) in the fourth, 1037 (72%) in the fifth, and 1020 (70%) in the sixth administration. In the control group, 999 (79%) of 1265 people participated in the mass drug administration." There was a fall in coverage in the intervention arm; however, as the control had no placebo, it is difficult to say if the deviations arose because of the trial context. They did not state whether they compared a per-protocol analysis or ITT analysis. It is very unlikely that entire clusters were analysed in the wrong group.
2.1b. If Y/PY/NI to 2.1a: were participants aware of their assigned intervention during the trial?	Y		
2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y		
2.3. If Y/PY/NI to 2.1 or 2.2: were there deviations from the intended intervention that arose because of the trial context?	NI		
2.4. If Y/PY to 2.3: were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA		
2.5a. Were any clusters or participants analysed in a group different from the one to which they were assigned?	NA		
2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI		
2.7. If N/PN/NI to 2.6: was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	N		
3.1a. Were outcome data available for all, or nearly all, clusters randomized?	Y	Some concerns	Data were available for all clusters randomized. 14 children were lost to follow-up from the control group and 10 from the intervention group. Data were available in all clusters.
3.1b. Were outcome data available for all, or nearly all, participants within clusters?	Y		
3.2. If N/PN/NI to 3.1: are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA		
3.3. If N/PN/NI to 3.1: is there evidence that results were robust to the presence of missing outcome data?	NA		
4.1. Was the method of measuring the outcome inappropriate?	N	Low risk	The method of measuring malaria incidence is acceptable in public health malaria trials. There was an objective protocol for measurement. The study was blinded only to the outcome assessor, who was allowed access only to the coded group and participant data when doing the initial
4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N		

Table 3. RoB 2 for cluster-randomized trials summary of judgments: adverse events *(Continued)*

4.3a. If N/PN/NI to 4.1 and 4.2: were outcome assessors aware that a trial was taking place?	Y		analyses. The outcome assessor was defined as the assessor conducting the analysis. It was unlikely that the awareness of the outcome assessor would have influenced the outcome measurement. Adverse events were reported to the study team. Adverse events were objective measures. They included all adverse events, whether related directly to the intervention or not. They were then analysed as being related to the intervention or not by the blinded study team.
4.3b. If Y/PY/NI to 4.3a: were outcome assessors aware of the intervention received by study participants?	Y		
4.4. If Y/PY/NI to 4.3b: could assessment of the outcome have been influenced by knowledge of intervention received?	PN		
4.5. If Y/PY/NI to 4.4: is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA		
5.1. Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	High risk	Statistical Analysis Plan and protocol available. Participants had repeated adverse events with multiple categorizations of severity and relation to the intervention. The data were not cluster adjusted. The analysis was by events rather than by the individuals. No adjustment of the result.
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...			
5.2. ...multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y		
5.3. ...multiple eligible analyses of the data?	Y		

Y: yes; N: no, PY: probably yes, PN: probably no, NI: no information

APPENDICES

Appendix 1. The effect of ivermectin treatment in humans on mosquito mortality: a systematic review of randomized controlled trials

Background

Our review question was whether ivermectin could reduce transmission in the community, but first, we wanted to establish its direct effect on mosquitoes. We sought the answer by summarising the data from randomized controlled trials (RCTs) of mosquito-feeding experiments in human participants treated with ivermectin.

Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 14 January 2021, Issue 1 of 12) in the Cochrane Library (searched 14 January 2021), MEDLINE Pubmed (1946 to 14 January 2021), Embase Ovid, (1974 to 14 January 2021), and Web of Science (searched 14 January 2021), using the search terms: ivermectin or avermectin or abamectin AND Anopheles or mosquitocid. We selected randomized trials that gave ivermectin at standard doses used for current mass drug administration (MDA) regimes to malaria-infected or healthy individuals. Our inclusion criteria were RCTs of healthy or malaria-infected people who had taken oral ivermectin, then given blood for membrane feeding or direct arm feeding on *Anopheles* species mosquitoes.

Two authors (RT and JO) independently reviewed the search results and agreed on selected articles for full-text review. To maintain consistency with the main review aims, we applied the same methods for data extraction and analysis as published in the main review protocol (de Souza 2018). The primary outcome for this review was mosquito mortality. Secondary outcomes included cumulative mortality rates, oocyte rates, and adverse event rates in humans.

Results

We identified 195 articles, of which we included five (Chaccour 2010; Derua 2015; Mekuriaw 2019; Ouédraogo 2015; Smit 2018); see Table 1 in this appendix.

Description of studies

All included studies reported mosquito mortality as their primary outcome. All studies used laboratory-reared mosquitoes. One trial recruited people with symptomatic *Plasmodium falciparum* infections (Smit 2018), one trial enrolled people with asymptomatic *P falciparum* infections (Ouédraogo 2015), and three trials recruited uninfected volunteers (Chaccour 2010; Derua 2015; Mekuriaw 2019; Table 1 in this appendix). Three of the studies used direct arm-feeding for mosquitoes (Chaccour 2010; Derua 2015; Mekuriaw 2019), while two studies used feeding membranes (Ouédraogo 2015; Smit 2018). Four studies used *An gambiae* (Chaccour 2010; Derua 2015; Ouédraogo 2015; Smit 2018), while one study each used *An funestus* (Ouédraogo 2015), and *An arabiensis* (Mekuriaw 2019) for the feeding experiments.

Mosquito mortality was reported differently in each study. In three studies, it was reported as a hazard ratio (Chaccour 2010; Ouédraogo 2015; Smit 2018). Three studies reported the mean cumulative daily mortality (Chaccour 2010 ; Derua 2015; Smit 2018), while Mekuriaw 2019 presented the mean daily mortality. Ouédraogo 2015 presented mosquito mortality data as geometric mean cumulative daily mortality.

Risk of bias

We assessed the risk of bias using the RoB 2 tool (Sterne 2019; see Table 2 in this appendix). We measured bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Apart from Smit 2018, prespecified statistical analysis plans were not available. As there were multiple outcome measurements and methods of statistical analyses used in the other four studies, we judged them as having a high risk of bias.

Effect on mortality

Overall, all studies showed large effects of ivermectin on mosquito mortality for variable periods, depending on the total dose of ivermectin given to human participants, the mosquito species, and day of blood meal post-treatment.

In the Smit 2018 study, the largest effect on mortality was seen when the blood meal was given two days after ivermectin ingestion of 600 µg/kg/day for three days (hazard ratio (HR) 12.58, 95% confidence interval (CI) 9.98 to 15.36), or 300 µg/kg/day for three days (HR 9.59, 95% CI 7.77 to 11.82; Table 3). The effect on mosquito mortality waned when the time period between ivermectin ingestion and feeds increased. The effect on day 28 was much lower; after 600 µg/kg/day for three days (HR 1.65, 95% CI 1.18 to 2.31), and 300 µg/kg/day for three days (HR 1.33, 95% CI 0.96 to 1.84; see Table 3 in this appendix).

Chaccour 2010 used a different dose of ivermectin and measured mortality at different time points, but found similar trends in mosquito mortality rates (Table 4). The largest effect was seen when the blood meal was given one day following a single dose of ivermectin 200 µg/kg/day (HR 2.22, 95% CI 1.83 to 2.7), which diminished by day 14 after a single dose of ivermectin 200 µg/kg/day (HR 1.07, 95% CI 0.87 to 1.31; Table 4).

Ouédraogo 2015 found a larger effect on *An funestus* mosquitoes following a single dose of ivermectin 200 µg/kg/day (HR 2.98, 95% CI 1.62 to 5.48), and ivermectin 200 µg/kg/day for three consecutive days (HR 9.07, 95% CI 5.06 to 16.25; Table 5), compared to the effect on *An gambiae* mosquitoes following a single dose of ivermectin 200 µg/kg/day (HR 1.37, 95% CI 1.14 to 1.65), and ivermectin 200 µg/kg/day for three days (HR 4.07, 95% CI 3.41 to 4.87; Table 6). The effect diminished by day seven in the *An gambiae* mosquitoes following a single dose of ivermectin 200 µg/kg/day (HR 0.93, 95% CI 0.79 to 1.11) and three days of ivermectin 200 µg/kg/day (HR 1.3, 95% CI 1.1 to 1.53; Table 5).

The data on cumulative mortality demonstrated a consistent and dose-dependent effect on mosquito mortality in the ivermectin arm (Tables 7 to 12). This effect on mortality decreased as the number of days between oral ivermectin the blood meal increased. Higher doses of ivermectin prolonged the effect, indicating an increased time of lethal concentration of ivermectin in the blood.

Conclusion

Ivermectin has a large effect on mosquito mortality. The effect is larger when mosquitoes feed soon after ivermectin administration, and when the dose of ivermectin is higher; the effect varies with mosquito species.

Table 1: Randomized controlled trials of the effect of oral ivermectin in humans on blood-fed mosquitoes

Trial	Population	Setting	Feeding method	Anopheles species	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Control group	Co-intervention	Day of mosquito feed after ivermectin administration
Mekuriaw 2019	Untested endemic setting	Ethiopia	Arm feeding	*An arabiensis*	175[a]	1	No drug	Nil	1, 4, 7, 10, 13
Derua 2015	Untested endemic setting	Tanzania	Arm feeding	*An gambiae*	150 to 200	1	Multivitamin	Nil	1
Chaccour 2010	Untested non-endemic setting	United Kingdom	Arm feeding	*An gambiae*	200	1	No drug	Nil	1, 14
Smit 2018	Tested and *P falciparum* positive; endemic setting	Kenya	Membrane feeding	*An gambiae*	300 or 600	3	Placebo	Dihydroartemisinin-piperaquine	0, 2, 7, 10, 14, 28
Ouédraogo 2015	Asymptomatic	Burkina Faso	Membrane feeding	*An gambiae* & *An funestus*	200	1 or 3	Placebo	Artemether-lumefantrine	1, 3, 7

[a]Given as standard dose, then calculated per kg; median value taken.

Table 2: Cochrane expanded risk of bias tool (studies with intention to treat)

Study ID	Random-ization process	Deviations from intended inter-ventions	Missing outcome data	Measure-ment of the outcome	Selection of the reported result	Overall
Ouédraogo 2015	+	+	+	+	--	-
Derua 2015	+	+	+	+	-	-
Smit 2018	+	+	+	+	+	+
Chaccour 2010	?	+	+	+	-	-
Mekuriaw 2019	+	+	+	+	-	-

Key: + Low risk; ? Some concerns; + High risk

Trials reporting Cox's proportional hazard ratio for mosquito mortality (Tables 3 to 6)

Table 3: The effect of ivermectin on mortality in *An gambiae* (Smit 2018)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Days of observation from ivermectin administration	HR (95% CI)	Control total mosquitoes	Control events by day 8 to 9 from blood meal	Assumed risk per 1000	Corresponding risk per 1000 (95% CI)
2	300	3	30	9.59 (7.77 to 11.82)	5039	1154	229	917 (868 to 954)
2	600	3	30	12.58 (9.98 to 15.36)	5039	1154	229	962 (925 to 982)
7	300	3	35	4.21 (3.06 to 5.79)	4277	1052	246	695 (579 to 805)
7	600	3	35	6.32 (4.61 to 8.67)	4277	1052	246	832 (728 to 914)
10	300	3	38	2.71 (1.85 to 3.97)	3726	1023	275	581 (448 to 720)
10	600	3	38	3.66 (2.51 to 5.33)	3726	1023	275	691 (553 to 819)
14	300	3	42	2.25 (1.6 to 3.16)	4043	1010	250	476 (369 to 597)
14	600	3	24	3.74 (2.67 to 5.26)	4043	1010	250	659 (536 to 780)
28	300	3	56	1.33 (0.96 to 1.84)	3991	1358	248	315 (239 to 408)
28	600	3	56	1.65 (1.18 to 2.31)	3991	1358	248	375 (285 to 482)

Key: HR**:** Cox's proportional hazard ratio; CI: confidence interval

Table 4: The effect of ivermectin on mortality in *An gambiae* (Chaccour 2010)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Days of observation from ivermectin administration	HR (95% CI)	Control total mosquitoes	Control events by day 8 to 9 from blood meal	Assumed risk per 1000	Corresponding risk per 1000 (95% CI)
1	200	1	13	2.22 (1.83 to 2.7)	250	179	716	939 (900 to 967)
14	200	1	26	1.07 (0.87 to 1.31)	N/A	N/A	N/A	N/A

Key: HR**:** Cox's proportional hazard ratio; CI: confidence interval; N/A: Not available

Table 5: The effect of ivermectin on mortality in *An funestus* (Ouedraogo 2015)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Days of observation from ivermectin administration	HR (95% CI)	Control total mosquitoes	Control events by day 8 to 9 from blood meal	Assumed risk	Corresponding risk per 1000 (95% CI)
1	200	1	10	7.12 (4.45 to 11.39)	N/A	N/A	N/A	N/A
3	200	1	10	2.98 (1.62 to 5.48)	N/A	N/A	N/A	N/A
3	200	3	10	9.07 (5.06 to 16.25)	N/A	N/A	N/A	N/A

Key: HR: Cox's proportional hazard ratio; CI: confidence interval; N/A: not available

Table 6: The effect of ivermectin on mortality in *An gambiae* (Ouedraogo 2015)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Days of observation from ivermectin administration	HR (95% CI)	Control total mosquitoes	Control events by day 8 to 9 from blood meal	Assumed risk	Corresponding risk per 1000 (95% CI)
1	200	1	11	3.86 (3.29 to 4.52)	N/A	N/A	N/A	N/A
3	200	1	13	1.37 (1.14 to 1.65)	N/A	N/A	N/A	N/A
3	200	3	13	4.07 (3.41 to 4.87)	N/A	N/A	N/A	N/A
7	200	1	17	0.93 (0.79 to 1.11)	N/A	N/A	N/A	N/A
7	200	3	17	1.3 (1.1 to 1.53)	N/A	N/A	N/A	N/A

Key: HR**:** Cox's proportional hazard ratio; CI: confidence interval; N/A: Not available

Studies reporting mosquito cumulative mosquito mortality per day (Tables 7 to 9)

Table 7: Effect of ivermectin on mortality in *An gambiae* (Chaccour 2010)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Days post-ivermectin	Experimental		Control		Experimental	Control
				Events	Total	Events	Total	Percentage mortality	Percentage mortality
1	200	1	3	194	267	78	250	72.7	31.2
			4	223	267	94	250	83.5	37.6
			5	236	267	110	250	88.4	44
			10	255	267	179	250	95.5	71.6

Table 8: Effect of ivermectin on mortality in *An gambiae* mosquitoes (Smit 2018)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (consecutive days)	Day post-ivermectin	Experimental		Control		Experimental	Control
				Events	Total	Events	Total	Percentage mortality	Percentage mortality
2	300	3	6	4353	5043	670	5039	86.3	13.3
			10	4851	5043	1154	5039	96.2	22.9
			14	4985	5043	2778	5039	98.9	55.1
	600		6	4183	4666	670	5039	89.7	13.3
			10	4458	4666	1154	5039	95.5	22.9
			14	4560	4666	2778	5039	97.7	55.1
7	300		11	2146	4239	586	4277	50.6	13.7
			15	3511	4239	1052	4277	82.8	24.6
			19	3941	4239	2336	4277	93	54.6
	600		11	3342	4763	586	4277	70.2	13.7
			15	4364	4763	1052	4277	91.6	24.6
			19	4610	4763	2336	4277	96.8	54.6
14	300		18	1037	3992	641	4043	26	15.9
			22	1948	3992	1010	4043	48.8	25
			26	2882	3992	2225	4043	72.2	55

(Continued)

	600	18	1645	4234	641	4043	38.9	15.9
		22	2617	4234	1010	4043	61.8	25
		26	3394	4234	2225	4043	80.2	55
28	300	40	2268	4007	2952	3991	56.6	74
	600	40	2268	4007	2307	3451	56.6	66.9

Table 9: The effect of ivermectin on mortality in *An gambiae* mosquitoes (Derua 2015)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Day post-ivermectin	Experimental		Control		Experimental	Control
				Events	Total	Events	Total	Percentage mortality	Percentage mortality
1	150 to 200	1	2	67.5	750	25.5	750	9	3.4
1	150 to 200	1	3	369	750	42	750	49.2	5.6
1	150 to 200	1	4	499.5	750	54	750	66.6	7.2
1	150 to 200	1	5	594	750	64.5	750	79.2	8.6
1	150 to 200	1	10	724.5	750	333	750	96.6	44.4
1	150 to 200	1	13	738	750	510	750	98.4	68

Studies that report mean daily mortality in mosquitoes

Table 10: The effect of ivermectin on *An arabiensis* mosquitoes (Mekuriaw 2019)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Day post-ivermectin	Experimental		Control		Experimental	Control
				Events	Total	Events	Total	Percentage mortality	Percentage mortality
1	175	1	6	55.2	304	7.4	160	18.2	4.6
3			8	44.76	324	6.92	16	13.8	4.1
7			12	4.74	84	2.85	89	5.6	3.2
12			17	2.52	81	2.73	85	3.1	3.2

Studies that report geometric mean cumulative mortality by day 10 (Table 11 and Table 12)

Table 11: The effect of ivermectin in *An gambiae* mosquitoes (Ouedrogo 2015)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Day post-ivermectin	Experimental		Control		Experimental	Control
				Events	Total	Events	Total	Percentage mortality	Percentage mortality
1	200	1	11	N/A	N/A	N/A	N/A	59.1	21.1
4		1	14	N/A	N/A	N/A	N/A	31.1	21.2
4		3	14	N/A	N/A	N/A	N/A	66.2	21.2
7		1	17	N/A	N/A	N/A	N/A	21.7	21.2
7		3	17	N/A	N/A	N/A	N/A	26.7	21.2

N/A: Not available

Table 12: The effect of ivermectin on *An funestus* mosquitoes (Ouedraogo 2015)

Day of blood meal post-ivermectin	Ivermectin dose (µg/kg/day)	Frequency of administration (days)	Day post-ivermectin	Experimental		Control		Experimental	Control
				Events	Total	Events	Total	Percentage mortality	Percentage mortality
1	200	1	11	N/A	N/A	N/A	N/A	40	5
4	200	1	14	N/A	N/A	N/A	N/A	10.9	5
4	200	3	14	N/A	N/A	N/A	N/A	51.4	5

N/A: Not available

Appendix 2. Detailed search strategies

Database: Cochrane Central Register of Controlled Trials

#1 malaria*:ti,ab,kw or plasmodium:ti,ab,kw (Word variations have been searched)

#2 anopheles:ti,ab,kw or mosquito*:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Ivermectin] explode all trees

#5 ivermectin:ti,ab,kw (Word variations have been searched)

#6 "abamectin":ti,ab,kw (Word variations have been searched)

#7 "avermectin":ti,ab,kw (Word variations have been searched)

#8 #4 or #5 or #6 or #7

#9 #3 and #8

Database: MEDLINE PubMed

Search	Query
#1	Search malaria Field: Title/Abstract
#2	Search "Malaria"[Mesh]
#3	Search "Plasmodium"[Mesh]
#4	Search plasmodium Field: Title/Abstract
#5	Search anopheles Field: Title/Abstract
#6	Search "Anopheles"[Mesh]
#7	Search mosquito* Field: Title/Abstract
#8	Search ((((((#7) OR #6) OR #5) OR #4) OR #3) OR #2) OR #1
#9	Search "abamectin" [Supplementary Concept]
#10	Search ivermectin Field: Title/Abstract
#11	Search "Ivermectin"[Mesh]
#12	Search avermectin Field: Title/Abstract
#13	Search abamectin Field: Title/Abstract
#14	Search ((((#13) OR #12) OR #11) OR #10) OR #9
#15	Search (#14) AND #8
#16	Search "Drug Therapy"[Mesh]

(Continued)

#17	Search randomly Field: Title/Abstract
#18	Search controlled clinical trial Field: Title/Abstract
#19	Search placebo or trial Field: Title/Abstract
#20	Search randomized controlled trial Field: Title/Abstract
#21	Search "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
#22	Search ((((#21) OR #20) OR #19) OR #18) OR #17 OR #16
#23	Search (#22) AND #15

Database: Embase (1947 to present, updated daily)

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1) malaria/ or malaria.mp.

2) Plasmodium/ or plasmodium.mp.

3) Anopheles/ or anopheles.mp.

4) mosquito*.mp. or mosquito/

5) 1 or 2 or 3 or 4

6) ivermectin/ or ivermectin.mp.

7) abamectin.mp. or abamectin/

8) avermectin.mp. or avermectin/

9) 6 or 7 or 8

10) 5 and 9

11) controlled clinical trial.mp. or Controlled Clinical Trial/

12) randomized controlled trial.mp. or Randomized Controlled Trial/

13) (randomized or placebo or double-blind* or single-blind*).mp.

14) randomization/

15) crossover procedure/

16) 11 or 12 or 13 or 14 or 15

17) 10 and 16

Database: LILACS

Search on: malaria or mosquito [Words] and ivermectin or abamectin [Words]

Web of Science

# 3	#2 AND #1

(Continued)

	Indexes=SCI-EXPANDED, Timespan=All years
# 2	TOPIC: (randomized trial or clinical trial) *OR* TOPIC: (double-blind* or single-blind* or placebo) *Indexes=SCI-EXPANDED, Timespan=All years*
# 1	TOPIC: (malaria or anopheles or mosquito*or plasmodium) *AND* TOPIC: (ivermectin or avermectin or abamectin) *Indexes=SCI-EXPANDED, Timespan=All years*

HISTORY

Protocol first published: Issue 9, 2018

CONTRIBUTIONS OF AUTHORS

DKD and RT screened the search results and extracted the data.

JB and CL analysed the data from the included study.

DAB contributed to the protocol stage. DKD, RT, and JO wrote the review draft.

All review authors revised and approved the final review version.

DECLARATIONS OF INTEREST

DKD has no known conflicts of interest.

RT has no known conflicts of interest.

JB is an investigator on the MASSIV and MATAMAL studies.

CL has no known conflicts of interest.

DAB has no known conflicts of interest.

JO has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine (LSTM), UK
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- MRC and Foreign, Commonwealth and Development Office (FCDO), UK

  JB received support from the UK MRC and the UK FCDO (#MR/R010161/1) under the MRC/FCDO Concordat agreement and as part of the EDCTP2.

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Irene Larbi stepped down from the review team. Rebecca Thomas, John Bradley, and Clemence Leyrat joined the review team.

We prioritized the review outcomes, focusing on outcomes in humans.

Prior to the screening process, we amended the protocol inclusion criteria to exclude studies using toxic sugar baits.

We were provided with the primary data by the study authors. We re-analysed the primary data using a Poisson mixed model with small sample size correction (Kenwood-Rodger), as well as cluster-level analysis using a linear weighted model in order to minimise the type 1 error rate (Kahan 2016).

We assessed risk of bias using the revised Cochrane risk of bias tool for randomised trials (RoB 2.0), with additional considerations for cRCTs, as this was deemed best able to summarise the biases particular to cluster trials (Eldridge 2021).

We included a nested systematic review of the randomized controlled trials examining the effect of ivermectin given to individually randomized people on mosquito mortality in the appendix.

As we only included one study in the review, we were unable to assess heterogeneity, reporting biases, synthesize data, or conduct sensitivity or subgroup analyses.